Figure 4d is a representative image of the plastic tube of Figure 4a using B-mode ultrasound of GOAM in oil;

Figure 5a is a representative image of a simulation illustrating total wave in the plane xz through the center of the sphere, from left to right, at a time of 11.5 microseconds;

Figure 5b is a representative image of the simulation of Figure 5a at a time of 17.3 microseconds;

Figure 5c is a representative image of the simulation of Figure 5a at a time of 23.1 microseconds;

Figure 5d is a representative image of the simulation of Figure 5a at a time of 38.4 microseconds;

Figure 6 illustrates RF acquisition data comparing GOAM of the present invention, albumin microspheres, and free Gd_2O_3;

Figure 7 illustrates ultrasonic attenuation comparing GOAM of the present invention, albumin microspheres, and free Gd_2O_3 at three separate concentrations;

Figure 8 illustrates integrated ultrasonic backscatter coefficient comparing GOAM of the present invention, albumin microspheres, and free Gd_2O_3 at three separate concentrations;

Figure 9 illustrates T_1 magnetic resonance enhancement by various contrast agents, including GOAM of the present invention; and

Figure 10 illustrates CT attenuation comparing GOAM of the present invention, water, albumin microspheres, free Gd_2O_3 at various concentrations, and stock solutions of commercially available contrast agents.

Banner & Witcoff, Ltd.
Ten South Wacker Drive
Chicago, IL 60606-7407

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to paramagnetic compositions for use with various imaging modalities. More particularly, the paramagnetic compositions of the present invention comprise one or more particles selected from the group consisting of gadolinium, zinc, magnesium, manganese, calcium and compounds thereof; and one or more microsphere shells encapsulating one or more particles, wherein the composition is effective for enhancing images obtained using more than one imaging modality as compared to images obtained without the composition. The GOAM of the present invention can be used as a contrast agent during medical diagnostic imaging procedures. The composition is used with imaging techniques, including ultrasound (US), magnetic resonance (MR), computed tomography (CT) and the like, to obtain enhanced images of a selected area of a patient's body. Use of the contrast agents of the present invention allows for examination of a patient by multiple imaging techniques, without the need for multiple contrast agents or additional patient preparation between techniques, to provide correlative studies for diagnostic purposes. A method of synthesizing such compositions also is provided. Although it is contemplated that contrast agents of the present invention may include microspheres that include compounds comprising metals, such as gadolinium, zinc, magnesium, manganese, calcium and the like, it will be described by way of example principally in connection with gadolinium oxide-containing protein microspheres.

As used herein, "contrast agent" and "imaging agent" relate to any composition administered *in vivo* to obtain images of an area of interest of a body. The images may be obtained using any imaging technique known in the art. Preferably, use of such agent

Banner & Witcoff, Ltd.
Ten South Wacker Drive
Chicago, IL 60606-7407

provides an enhanced image of the body structures within the area of interest as compared to an image obtained without use of any such agent.

As used herein, "microsphere" means any microbubble within a solution, the microbubble having an average diameter of no greater than about 7μm, and more preferably between about 0.5 and about 4μm. Generally, a microsphere may be gas-filled, aqueous or non-aqueous solution-filled and/or include particulate matter in its outer shell. Preferably, in accordance with the invention, the microsphere contains particulate matter.

As used herein, "paramagnetic compound" is intended to refer to a compound that enhances the relaxation of hydrogen protons in body tissue during MR imaging. Such a compound improves T_1 and T_2 relaxation time and readily brightens tissues in which the compound becomes localized.

Figure 1 illustrates a typical air-in-oil (unshelled) microbubble, as known in the art. The oil solution was first sonicated and then air bubbles were created in the oil by blowing in air. Figure 2 shows a prior art albumin microsphere. Similar microspheres and liposomes have been used as contrast agents with US with limited benefits. The oil microsphere of Figure 1 and the albumin microsphere of Figure 2 do not have the physical and functional characteristics required to provide enhancement if used with other imaging modalities, such at MR and CT.

As shown in Figure 3, in accordance with the present invention, a composition of gadolinium oxide-containing albumin microspheres ("GOAM") is provided for use as a contrast agent. The contrast agent includes a high-density paramagnetic particle incorporated by polymerization in a protein shell. Preferably, the gadolinium is provided as Gd_2O_3

Banner & Witcoff, Ltd.
Ten South Wacker Drive
Chicago, IL 60606-7407